

REMARKS

As a preliminary matter, Applicants note that copies of the references listed on the IDS filed December 3, 2001, and crossed out by the Examiner (see Paper No. 4), were resubmitted with the Amendment A and Response filed on April 30, 2002. However, the Office has not yet indicated whether these references have been made of record in the subject application.

Status of the claims

Claims 8-10, 17-30, 33-34, 39, 42-91, 96-98, 100 and 102-105 have been cancelled without prejudice to pursuing these claims in a continuation application.

Thirty-five of the original claims, claims 1-8, 11-16, 31-32, 35-38, 40, 41, 92, 94, 99, 101, and 105-113 are pending, and stand rejected under 35 U.S.C. §112, first paragraph. Claim 1 has been amended to correct an obvious grammatical error. Claims 5, 7, 31, and 101 have been rewritten as independent claims. Claims 6 and 93 have been amended to depend from claim 5. Claims 8 and 105 have been cancelled, as noted above. Claim 95 has been amended to depend from claim 7.

New claims 114-124 have been added. Support for these claims may be found, for example, in originally filed claims 99 and 106-113; page 10, line 14 through page 13, line 13 of the specification; and page 36, line 16 through page 39, line 24 of the specification.

No new matter has been added by these amendments.

Section 112, first paragraph rejection

Reconsideration is requested of the rejection of claims 1-8, 11-16, 31-32, 35-38, 40, 41, 92, 94, 99, 101, and 105-113 under §112, first paragraph.

As noted above, claims 8 and 105 have been cancelled,

rendering moot their rejection.

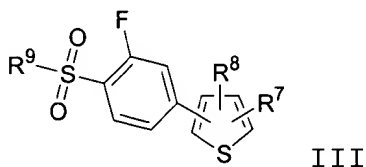
The Office asserts that the specification does not reasonably provide enablement for the radicals A in Formula I equal to all 5- or 6-membered heterocyclic rings. It is noted that the Office has not raised any issue with respect to enablement when A is selected to be a partially saturated or unsaturated carbocyclic ring.

For purposes of discussion, the pending claims will be discussed in four sets: a) independent claim 31 and dependent and related claims; b) independent claim 7 and dependent and related claims; c) independent claim 5 and dependent and related claims; d) independent claim 1 and dependent and related claims.

Each of the separate sets satisfies the requirements of §112, first paragraph for distinct reasons.

a) Claims 31-32, 35-38, 40-41, 94, 101, and 114-122 are enabled by the specification

Claim 31, as amended, is directed to compounds of Formula III



or their pharmaceutically-acceptable salts, tautomers or prodrugs, wherein R⁷, R⁸ and R⁹ are as defined in the claim. Compounds of Formula III specifically require a thiophene group rather than the broader A in Formula I of claim 1.

The Office action states that all the claims, including claim 31, are not enabled because "the specification does not reasonably provide enablement for the radicals A equal to all 5 or 6 membered heterocyclic rings." But claim 31 does not encompass compounds where A is equal to "all 5 or 6 membered heterocyclic rings." Rather, claim 31 specifically requires a

thiophene group.

In view of the fact that claim 31 specifically requires a thiophene group at the relevant position, claim 31 is enabled by the specification. Schemes V-VII beginning at page 128 describe preparation of intermediates useful in the preparation of such thiophene-containing compounds, and Schemes VIII-XI describe the preparation of the thiophene-containing compounds themselves. Examples 1 and 2 beginning at page 157 detail the preparation and characterization of compounds within the scope of claim 31.

The Federal Circuit has stated that a specification must be taken as in compliance with the enablement requirement of §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support.¹ As stated in MPEP 2164.04 citing the Federal Circuit decision in In re Wright, the Office "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention," which requires the Office to provide "a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure." In the present situation, the Office has provided no explanation that the compounds of claim 31 wherein the subject radical is the stated thiophene-containing compounds are not adequately enabled. In fact, Schemes V-XI and Examples 1 and 2 are so specifically enabling of claim 31 that it is respectfully submitted that such a statement could not fairly be made. Likewise, for the same reasons, the Office has not set forth a case of non-enablement with respect to claims 32, 35-38, 40, or 41, all of which depend from claim 31.

Claim 94, as amended, is directed to a pharmaceutical composition comprising a therapeutically-effective amount of a

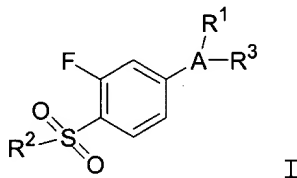
¹ See, e.g., In re Marzocchi, 439 F.2d 220, 223-24 (CCPA 1971); see also MPEP 2164.04.

compound of claim 31. These pharmaceutical compositions are described in detail in the specification.² One skilled in the art could readily prepare such compositions, given this disclosure and the disclosure discussed above with respect to claim 31, without undue experimentation. Thus, claim 94 is enabled by the specification.

Similarly, claim 101, which is directed to a method of treating inflammation comprising administering a therapeutically-effective amount of a compound of Formula III (defined as above for claim 31), is enabled by the specification. In addition to the synthetic schemes noted above (i.e., Schemes VIII-XI, which describe the preparation of compounds of Formula III), the specification describes compounds of Formula III as COX-2 inhibitors and provides experimental data showing their efficacy as such.³ Again, the Office has presented no explanation that casts doubt that these schemes, examples, and *in vitro* results fully enable the synthesis and claimed use of these thiophene-containing compounds, and thus has failed to make a *prima facie* case that claim 101 does not meet the enablement requirement of §112, first paragraph. Likewise, new claims 114-121, which depend from claim 101, are enabled by the specification.

b) Claims 7, 95, and 124 are enabled by the specification

Claim 7 is directed to a compound of Formula I



or their pharmaceutically-acceptable salts, tautomers or prodrugs, wherein A is a radical selected from the six-member

² See page 118, line 24 through page 121, line 23.

³ See, e.g., Table I and II, specifically the entries for Examples 1 and 2.

Markush group consisting of thienyl, furanone, isoxazolyl, pyrazolyl, cyclopentenyl and pyridinyl; and R¹, R², and R³ are as defined in the claim.

The Office action states that all the claims, including claim 7, are not enabled because "the specification does not reasonably provide enablement for the radicals A equal to all 5 or 6 membered heterocyclic rings." But claim 7 does not encompass compounds where A is equal to "all 5 or 6 membered heterocyclic rings." Rather, claim 7 specifically requires A is a radical selected from the six-member Markush group consisting of thienyl, furanone, isoxazolyl, pyrazolyl, cyclopentenyl and pyridinyl; and R¹, R², and R³ are as defined in the claim. The Office has not raised any issue with respect to enablement when A is selected to be one of these specific partially saturated or unsaturated carbocyclic ring such as cyclopentenyl.

In view of the fact that claim 7 specifically requires one of these six specific compounds at the relevant position, claim 7 is enabled by the specification. In particular, the specification provides over thirty synthetic schemes for the preparation of the fluoro-substituted benzenesulfonamides of Formula I generally, as well as for the preparation of particular classes of compounds within the scope of Formula I having a diverse range of heterocyclic groups for A, in addition to intermediates useful in their preparation.⁴ Also provided are twenty-four examples illustrating the preparation of particular species within the scope of Formula I.⁵ Furthermore, the specification lists a number of references describing related compounds having a multitude of heterocyclic ring groups, including thienyl, furanonyl, isoxazolyl, pyrazolyl, and

⁴ See Schemes I-XXXVI.

⁵ See Examples 1-24.

pyridinyl,⁶ i.e., each of the heterocyclo groups in the definition of A in claim 7.

The synthetic schemes, examples, and prior art described above illustrate the preparation of compounds comprising each of the heterocyclic radicals in the definition of A in claim 7; adapting these schemes to prepare compounds according to claim 7 would be a routine matter for one of ordinary skill in the art, i.e., the adaptation could be accomplished without undue experimentation.

The Federal Circuit has stated that a specification must be taken as in compliance with the enablement requirement of §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support.⁷ As stated in MPEP 2164.04 citing the Federal Circuit decision in In re Wright, the Office "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention," which requires the Office to provide "a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure." In the present situation, the Office has provided no statement or explanation that the compounds of claim 7 wherein the subject substituent is selected from the stated Markush group are not adequately enabled. In fact, the aforementioned passages in the specification are so specifically enabling of claim 7 that it is respectfully submitted that such a statement could not fairly be made.

Claim 95, as amended, is directed to a pharmaceutical composition comprising a therapeutically-effective amount of a compound of claim 7. These pharmaceutical compositions are

⁶ See, e.g., page 2, line 16 through page 5, line 11.

⁷ See, e.g., In re Marzocchi, 439 F.2d 220, 223-24 (CCPA 1971); see also MPEP 2164.04.

described in detail in the specification. One skilled in the art could readily prepare such compositions, given this disclosure and the disclosure discussed above with respect to claim 1, without undue experimentation. Thus, claim 95 is enabled by the specification.

New claim 124 is directed to a method of treating inflammation comprising administering a therapeutically-effective amount of a compound of Formula I, wherein A is defined as shown above for claim 7, and R¹, R², and R³ are as defined in the claim. The specification describes these methods in detail, and further provides *in vitro* data regarding the COX-1 and COX-2 activities of these compounds. In light of this disclosure, and for the reasons given above with respect to claim 7, claim 124 is enabled by the specification.

c) Claims 5-6, 11-16, 93, and 123 are enabled by the specification

Claim 5, as amended, is directed to a compound of Formula I as shown above, or their pharmaceutically-acceptable salts, tautomers or prodrugs, wherein A is a radical selected from the nineteen-member Markush group consisting of thienyl, furyl, furanone, thiazolyl, oxothiazolyl, thioxothiazolyl, imidazolyl, benzofuryl, indenyl, benzothienyl, isoxazolyl, oxooxazolyl, pyrazolyl, cyclopentenyl, cyclopentadienyl, benzindazolyl, benzopyranopyrazolyl, phenyl, and pyridyl; and R¹, R², and R³ are as defined in the claim.

The Office action states that all the claims, including claim 5, are not enabled because "the specification does not reasonably provide enablement for the radicals A equal to all 5 or 6 membered heterocyclic rings." But claim 5 does not encompass compounds where A is equal to "all 5 or 6 membered heterocyclic rings." Rather, claim 5 specifically requires A is

a radical selected from the stated nineteen-member Markush group; and R¹, R², and R³ are as defined in the claim.

The specification provides over thirty synthetic schemes for the preparation of the fluoro-substituted benzenesulfonamides of Formula I generally, as well as for the preparation of particular classes of compounds within the scope of Formula I having a diverse range of heterocyclic groups for A, in addition to intermediates useful in their preparation. The specification includes twenty-four examples illustrating the preparation of particular species within the scope of Formula I as defined by claim 5, and lists numerous references describing related compounds having a multitude of heterocyclic ring groups (including oxazolyl, oxazolonyl, pyrrolyl, pyrazolyl, imidazolyl, furanonyl, isoxazolyl, pyrazolyl, thienyl, furyl, pyridinyl, thiazolyl, imidazolyl, benzimidazolyl, indanonyl, benz[g]indazolyl, benzopyranyl, benzopyranopyrazolyl, and heteroarylpyranopyrazolylyls). One skilled in the art, equipped with this detailed disclosure of the instant specification, and familiar with basic synthetic organic chemistry, could readily adapt the synthetic schemes and examples described in the specification to prepare compounds within the scope of Formula I as defined in claim 5, having heterocyclic groups for A within the limited number in the Markush group, but different from those specifically described in the schemes. Such adaptation is clearly within the abilities of one skilled in the art, and while some experimentation may be needed, such experimentation could be routinely performed by the skilled artisan, i.e., the adaptation could be accomplished without undue experimentation.

The synthetic schemes and examples described above illustrate the preparation of compounds comprising most of the radicals within the definition of A in claim 5; adapting these schemes (particularly in light of the prior art; see, e.g., page

2, line 16 through page 5, line 11 of the specification) to prepare compounds having A equal to heterocyclic not specifically exemplified would be a routine matter for one of ordinary skill in the art.

The Federal Circuit has stated that a specification must be taken as in compliance with the enablement requirement of §112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for the enabling support.⁸ As stated in MPEP 2164.04 citing the Federal Circuit decision in In re Wright, the Office "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention," which requires the Office to provide "a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure." In the present situation, the Office has provided no statement or explanation that the compounds of claim 5 wherein the subject substituent is selected from the stated Markush group are not adequately enabled. In fact, the aforementioned passages in the specification are so specifically enabling of claim 5 (and claims 6, 11-16) that it is respectfully submitted that such a statement could not fairly be made. Thus claim 5, and dependent claims 6 and 11-16, are enabled by the specification.

Claim 93, as amended, is directed to a pharmaceutical composition comprising a therapeutically-effective amount of a compound of claim 5. These pharmaceutical compositions are described in detail in the specification. One skilled in the art could readily prepare such compositions, given this disclosure and the disclosure discussed above with respect to claim 5, without undue experimentation. Thus, claim 93 is enabled by the

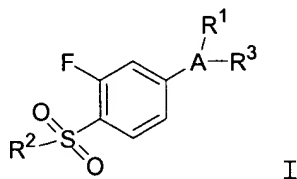
⁸ See, e.g., In re Marzocchi, 439 F.2d 220, 223-24 (CCPA 1971); see also MPEP 2164.04.

specification.

New claim 123 is directed to a method of treating inflammation comprising administering a therapeutically-effective amount of a compound of Formula I, wherein A is defined as shown above for claim 5, and R¹, R², and R³ are as defined in the claim. The specification describes these methods in detail, and further provides *in vitro* data regarding the COX-1 and COX-2 activities of these compounds. In light of this disclosure, and for the reasons given above with respect to claim 5, claim 123 is enabled by the specification.

d) Claims 1-4, 92, 99, and 106-113 are enabled by the specification

Claim 1 is directed to compounds of Formula I:



or their pharmaceutically-acceptable salts, tautomers or prodrugs, wherein A is a 5- or 6-member ring substituent selected from partially saturated or unsaturated heterocyclic and carbocyclic rings, and R¹, R² and R³ are as defined in the claim.

The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information generally available to those skilled in the art without undue experimentation. The mere fact that some experimentation may be necessary to select and prepare compounds having a 5- or 6-membered partially saturated or unsaturated heterocyclic ring substituent not named in the specification does not render the specification non-enabling. As stated by the Board of Patent Appeals:

The determination of what constitutes undue experimentation

in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.⁹

Furthermore, as noted above, patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.

In the Wands case cited in the Office action, the claim at issue required using an antibody "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$." 8 USPQ2d p. 1402. The Federal Circuit discussed several of the relevant factors and concluded that "undue experimentation would not be required to practice the invention." 8 USPQ2d 1406.

With regard to the factor of "the amount of direction provided by the inventor," the Federal Circuit concluded that Wands provided "significant guidance and direction on how to practice the invention and present[ed] working examples." The Wands patent (4,879,219) is 18 columns long, including two columns of claims. Applicants' present specification is 196 pages long prior to the claims, including 75 pages (121-196) devoted to synthesis, working examples, and screening. The present specification provides over thirty synthetic schemes for the preparation of the fluoro-substituted benzenesulfonamides of Formula I generally, as well as for the preparation of particular classes of compounds within the scope of Formula I having a

⁹ Ex parte Forman, 230 U.S.P.Q. 546, 547 (BPAI 1986); see also MPEP 2164.06.

diverse range of heterocyclic groups for A, in addition to intermediates useful in their preparation. The specification lists twenty-four examples illustrating the preparation of particular species within the scope of Formula I. The specification reports references describing related compounds having a multitude of heterocyclic ring groups (including oxazolyl, oxazolonyl, pyrrolyl, pyrazolyl, imidazolyl, furanonyl, isoxazolyl, pyrazolyl, thiophenyl, furyl, pyridinyl, thiazolyl, imidazolyl, benzimidazolyl, indanonyl, benz[g]indazolyl, benzopyranyl, benzopyranopyrazolyl, and heteroarylpyranopyrazolyls). One skilled in the art, equipped with the detailed disclosure of the instant specification, and familiar with basic synthetic organic chemistry, could readily adapt the synthetic schemes and examples described in the specification to prepare compounds within the scope of Formula I, having different heterocyclic groups for A than those specifically described in the schemes. Such adaptation is clearly within the abilities of one skilled in the art, and while some experimentation may be needed, such experimentation could be routinely performed by the skilled artisan, i.e., the adaptation could be accomplished without undue experimentation.

With regard to "the level of skill," the Federal Circuit stated "There was a high level of skill in the art at the time when the application was filed." 8 USPQ2d 1406. In the present situation, the level of skill of pharmaceutical chemists in the field of chemical synthesis is similarly high.

With regard to "the nature of the invention," the Federal Circuit in Wands stated that

"the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody."

Similarly in the present case, the nature of the invention requires reasonable screening, and pharmaceutical chemists in the field of chemical synthesis are prepared to screen compounds falling within the claim scope.

With regard to "working examples," Wands conducted just ten fusion experiments to produce hybridomas having the required binding affinity (8 USPQ2d 1405), and carried out the entire synthesis and screening procedure just three times. 8 USPQ2d 1407. The present specification provides 24 detailed working examples of syntheses and 24 sets of "Biological Evaluation" (p.192). This cannot fairly be deemed to favor a finding of non-enablement.

With regard to "state of the art," the state of the art is especially well developed in the fields of chemical synthesis and screening for pharmaceutical activity.

With regard to the "breadth of the claims," the Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four (8 USPQ2d 1405), not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$." This breadth, deemed acceptable, is much broader than a claim limited to those antibodies Wands produced or tested. Against this background, applicants respectfully submit that the breadth of their claims is reasonable in light of the 196 pages of explanatory specification including 75 pages devoted to synthesis, working examples, and screening.

With regard to the "level of predictability," the Federal Circuit in Wands noted that viewing the data as proposed by the Board, only four of 143 of Wands' hybridomas, or 2.8% of those

produced (not even considering those not produced), were proven to have the activity required by the claims. 8USPQ2d 1405. In the present specification many more than candidates than four were tested (24; see Biological Evaluation, p. 192 ff.), and screening according to the procedures well documented in the specification is well within the ordinary skill in the art.

With regard to the "quantity of experimentation," in Wands nine of 143 hybridomas were tested, and four were determined to have the required activity. This left 130+ hybridomas produced untested, as well as countless others not even produced. The present applicants should similarly not be precluded from patent protection on the basis they have left a considerable quantity of compounds untested, because, as stated by the Board:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.¹⁰

Patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.¹¹

For the foregoing reasons, claim 1 is enabled by the specification. Similarly, claims 2 and 3, which depend from claim 1, are also enabled by the specification.

Claim 4 depends from claim 1 and defines A as a 5- or 6-membered ring substituent selected from partially saturated or unsaturated carbocyclic rings. As noted above, claims 1-8, 11-16, 31-32, 35-38, 40, 41, 92, 94, 99, 101, and 106-113 were rejected

¹⁰ Ex parte Forman, 230 U.S.P.Q. 546, 547 (BPAI 1986); see also MPEP 2164.06.

¹¹ In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

because, the Office asserts, the specification does not reasonably provide enablement for the radicals A equal to all 5 or 6 membered heterocyclic rings. However, claim 4 does not define A to include any heterocyclic rings, and thus the Office has not established a basis by which claim 4 could be considered to be non-enabled. The specification includes two synthetic schemes, XXXII and XXXIII, which illustrate the preparation of representative carbocyclic rings. One skilled in the art could readily adapt these schemes to prepare compounds having other 5- or 6-membered carbocyclic rings. The Office has presented no evidence or reasoning inconsistent with this, and thus has not shown that claim 4 is not enabled by the specification.

Claim 92 is directed to a pharmaceutical composition comprising a therapeutically-effective amount of a compound of claim 1. These pharmaceutical compositions are described in detail in the specification. One skilled in the art could readily prepare such compositions, given this disclosure and the disclosure discussed above with respect to claim 1, without undue experimentation. Thus, claim 92 is enabled by the specification.

Claim 99 is directed to a method of treating inflammation comprising administering a therapeutically-effective amount of a compound of Formula I, defined as shown above for claim 1. The specification describes these methods in detail, and further provides *in vitro* data regarding the COX-1 and COX-2 activities of these compounds. In light of this disclosure, and for the reasons given above with respect to claim 1, claim 99, and claims 105-113, which depend from claim 99, are enabled by the specification.

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PHA 4176 (3364/1)
PATENT

Conclusion

In light of the foregoing remarks, it is respectfully submitted that the pending claims satisfy the requirements of §112, first paragraph. Favorable reconsideration and early allowance of all claims are respectfully requested.

If there are any additional charges in this matter, please charge Deposit Account No. 19-1345.

Respectfully submitted,



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